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Longitudinal verbal fluency in normal aging, preclinical and prevalent Alzheimer disease

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Abstract

Background—Few longitudinal studies evaluate differences in patterns of change of category compared to letter fluency across the spectrum of cognitive impairment.

Methods—We compared change in category (animal and supermarket) and letter (F,A,S) fluency among 239 participants in three groups: remained cognitively normal throughout follow-up (n=96), developed AD (preclinical AD, n=21), and with AD at initial testing (prevalent AD, n=122).

Results—At baseline, prevalent and preclinical AD groups scored lower on animal than letter fluency. On all fluency measures, the prevalent AD declined faster than other groups (all $p < 0.0001$), and preclinical AD declined faster than unimpaired (all $p \leq 0.02$). Overall, animal fluency declined faster than letter fluency; animal fluency declined significantly faster than letter fluency among cognitively normal and prevalent AD subjects.

Conclusion—Greater longitudinal declines in category compared to letter fluency are consistent with cross-sectional studies. Steeper declines on both fluency measures distinguish preclinical AD from cognitively unimpaired individuals.

Keywords

dementia; neuropsychology; fluency; Alzheimer disease; semantic memory; cognitive impairment

Introduction

Tests of verbal fluency draw on both executive function and language abilities, and provide good discrimination between persons with normal cognitive function compared to those with mild Alzheimer disease (AD) (1). Although tests of verbal fluency can include either category fluency or letter fluency, it is now well established that category fluency is superior to letter fluency in distinguishing between normal controls and AD patients, even in the mild stages of dementia (1-7). While both category and letter fluency tasks are used to assess retrieval of

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language, this discrepancy has been attributed to selective deterioration of semantic networks evident in earlier stages of AD (8).

It has further been shown that category fluency distinguishes normal controls from subjects diagnosed as either cognitively impaired but not demented (CIND) or as mild cognitive impairment (MCI) (9,10). Finally, baseline impairments in category fluency predict who subsequently will develop AD (11-13). A recent review (2) reported that 29 of 32 studies found that category fluency distinguished normal elderly from MCI or preclinical dementia while 17 of 17 studies found that category fluency distinguished between MCI or preclinical dementia and AD. On letter fluency performance, when comparing normal elderly to MCI, or MCI to AD, an equal number of studies reported no differences as reported differences. Importantly, the majority of these reports have used cross-sectional comparisons of test performance.

In contrast to these cross-sectional studies, only a few longitudinal studies have examined comparative rates of change in category compared to letter fluency in persons with AD, in persons who subsequently develop AD, or among persons who are cognitively intact. One study found that AD participants showed more rapid decline at 1-year follow-up in category fluency compared to cognitively intact participants, while showing little change in letter fluency in the same time period (14). In the MoVIES study, there was significant decline over two years on categorical but not on letter fluency prior to dementia onset (15). In the Paquid study, both non-demented and preclinical AD samples declined on categorical fluency over a 9-year period, with faster decline in the preclinical group during the years just prior to AD onset (13,16).

The purpose of our study was to evaluate longitudinal change over multiple times of measurement across groups of persons with AD, a preclinical AD sample, and normal controls. We compared rates of change in verbal (category and letter) fluency among three samples of participants in an ongoing longitudinal study with repeated neuropsychological testing. The three samples were: (1) normal cognitive function throughout follow-up (cognitively normal), (2) initially normal cognitive function but later developing AD (preclinical AD), and (3) AD at initial testing (prevalent AD). We hypothesized that: (1) both letter and category fluency would differentiate subject groups, both cross-sectionally and longitudinally, and (2) performance on category fluency would be more impaired than performance on letter fluency within both AD groups, both cross-sectionally and longitudinally.

Methods

Study design and participants

Participants were enrolled in a longitudinal study of aging and dementia at the University of Southern California Alzheimer Disease Research Center (ADRC). Informed consent was obtained from all participants or their caregivers using procedures approved by the Institutional Review Board at the University of Southern California.

Inclusion criteria for the longitudinal study were: Los Angeles area residents at least 60 years old and willing to participate in periodic cognitive reassessment. Persons with a history of stroke, or other neurological, metabolic, or neoplastic disorders which might produce dementia symptoms, a recent history of heavy alcohol use, or a history of hospitalization for depression were excluded from participation.

At enrollment, each participant received neuropsychological testing. The neuropsychological test battery was completed at scheduled intervals throughout follow-up and was administered by trained psychometrists. For participants with dementia, clinical diagnosis was determined at a consensus conference, following neurological, neuropsychological, and medical

examinations. AD was diagnosed according to the Diagnostic and Statistical Manual for Mental Disorders, 3rd edition–revised (DSM-III-R) criteria for dementia (APA, 1987) and NINCDS-ADRDA criteria for AD (17). Dementia severity was graded using the Clinical Dementia Rating Scale (CDR) (18), a 5-point scale used to discriminate individuals without dementia (0), with questionable (0.5), or with mild (1), moderate (2), or severe (3) dementia. Demented participants were re-tested at six-month to one-year intervals, while non-demented participants were re-tested at one- to two-year intervals.

Study groups

Eligible participants were categorized into three study groups for the purposes of this analysis. (1) cognitively normal– participants were unimpaired (CDR=0) throughout the follow-up period of this analysis. (2) preclinical AD – participants were not demented at initial testing, but had a final diagnosis of AD during the follow-up period of this analysis. In the preclinical AD group, only those neuropsychological tests prior to the onset of dementia (CDR<1) were included in the analysis. (3) prevalent AD – participants were demented (with an AD diagnosis) at initial testing with $CDR \leq 2$. A total of 239 participants (96 cognitively normal, 21 preclinical AD, and 122 prevalent AD) with at least two times of testing during the follow-up were included in the current analysis.

Verbal fluency measures

The neuropsychology battery included an array of tests assessing memory, language, visuo-spatial, and executive performance. A depression scale was also completed. To assess letter fluency, participants were asked to name as many words as possible starting with the letters F, A, and S, with 60 seconds allowed for each letter. A total letter fluency score was used in the analyses, based on the sum of correct and novel responses over the three letter trials. Category fluency was assessed by asking participants to name as many animals as possible in 60 seconds; a second 60-second task required participants to name items they would find in a supermarket. Separate scores for both animal and supermarket category fluency were used in the analyses, each based on the number of correct and unique responses provided over 60 seconds.

Statistical analysis

Each measure of verbal fluency (letter, animal, supermarket) was standardized by the mean and SD of the cognitively unimpaired group (using data from the sample's initial testing to generate the mean and SD), enabling direct comparison across tests. Sample demographic characteristics and mean baseline verbal fluency measures were compared among the three study groups using analysis of variance (ANOVA).

We fitted separate mixed effects linear regression models for the standardized letter, animal and supermarket fluency scores to compare the performance of each measure of verbal fluency among the study groups (19). These longitudinal models allowed us to compare fluency among study groups both cross-sectionally (mean baseline score) and longitudinally (annual rate of change). Study group was modeled as a fixed effect, while time (in years) since the first testing occasion was included as a random effect. The main effect of study group tested the cross-sectional group differences in the fluency measure, while an interaction term of group-by-time tested whether the annual rate of change in the fluency measure differed across groups. These models involving group comparisons controlled for age at the first neuropsychological testing, gender, education, and the interaction of these variables with time.

To test if letter fluency differed from category fluency within study group, separate mixed effects models were fitted for each group to compare the mean baseline scores and the annual rates of change between the standardized fluency measures. An indicator variable for fluency measure (letter, animal, supermarket) was modeled as a fixed effect, while time since the first

testing occasion was modeled as a random effect. The main effect of fluency measure tested if the fluency measures (letter vs. category) differed in cross-sectional comparisons. An interaction term of fluency measure-by-time tested if the rates of change differed across the fluency measures. Because these statistical comparisons among fluency measures occurred within subjects, we did not adjust for demographic factors. In addition to accounting for correlated measures due to repeated testing within participants, major advantages of the mixed model approach include the flexible handling of different numbers of testings and different inter-test intervals among participants. All statistical testing was performed at a two-sided 5% level of significance and used Statistical Analysis System version 9.1 software (SAS Institute, Cary, NC); analyses with mixed effects models used SAS PROC MIXED.

Results

Study sample

Table 1 describes the sample used in this study, by study group. The sample was primarily white, 60% female and on average had more than a high school education. The average follow-up among the study groups ranged from 2.3 to 5.9 years, and the average number of times of testing ranged from 4.5 to 6.3 tests (Table 1). Participants with AD at initial testing were on average 4.9 years since onset of dementia (range 0.5-16 years). The initial testing of participants who developed AD during follow-up was on average 5.4 (range 0.5-9.6) years prior to diagnosis.

Cross-sectional associations of study group with verbal fluency

Table 2 and Figure 1 display the results of group comparisons on standardized verbal fluency scores using mixed model analyses. The cross-sectional analysis represents the average fluency scores at initial testing. After adjusting for age, education and gender, the three groups significantly differed on all measures of verbal fluency (all $p < 0.0001$). The average performance of the preclinical AD group lay between the cognitively normal and prevalent AD groups on all three fluency measures. Cross-sectionally, the prevalent AD group scored significantly lower than the preclinical AD group and significantly lower than the cognitively normal group on all fluency measures (all $p < 0.001$). The preclinical AD group scored significantly lower than the cognitively normal group only on animal fluency ($p = 0.003$). The magnitude of the difference between mean scores shown in Table 2 corresponds to the number of standard deviation units. Thus, participants who developed AD scored lower than the cognitively normal group on initial animal fluency by an average of 0.50 standard deviation units.

Table 3 displays the comparison of average performance on each of the three standardized fluency measures within study group using mixed model analyses. The cross-sectional analyses compare the relative performance on the three fluency measures at the initial testing. In cognitively normal participants, higher animal fluency was observed when compared to letter fluency ($p = 0.02$). As expected and consistent with prior studies, participants with prevalent AD performed significantly worse on both animal and supermarket fluency compared to letter fluency ($p < 0.0001$ for both tests), with performance on animal fluency not significantly different from supermarket fluency. In preclinical AD participants, the average initial performance among the fluency measures did not significantly differ overall ($p = 0.11$ among tests); however, the average animal fluency standard score was significantly lower than letter fluency ($p = 0.04$). In this preclinical AD group, average supermarket fluency did not differ significantly from either letter or animal fluency.

Longitudinal associations of study group with verbal fluency

Table 2 and Figure 2 also summarize mixed model results comparing the study groups on the annual rates of change on the standardized fluency measures, adjusted for age, education and gender. The average change rates significantly differed among the study groups on all three fluency measures (all $p < 0.0001$). On all fluency measures, the prevalent AD group declined at a significantly faster rate than the preclinical AD group and than the cognitively normal group (all $p < 0.02$). The preclinical AD group also declined at a significantly faster rate than the cognitively normal group on all fluency measures (all $p < 0.02$).

Table 3 also summarizes mixed model results comparing the annual rates of change among the three fluency measures, by study group. In cognitively normal participants, the rates of change significantly differed among the three fluency measures ($p = 0.01$). Animal fluency on average declined at a faster rate than letter fluency ($p = 0.003$). Change in supermarket fluency did not significantly differ from either letter or animal fluency change rates. Rates of change among the three fluency measures also differed significantly in the prevalent AD group ($p < 0.0001$). Both animal fluency and supermarket fluency declined on average at a faster rate than letter fluency (both $p < 0.001$); rates of decline in animal and supermarket fluency did not significantly differ. In participants with preclinical AD, the average annual change rates on all fluency measures showed significant decline but did not differ from one another ($p = 0.49$ for difference among measures).

Discussion

In this longitudinal analysis, our sample included participants with a range of cognitive impairment, encompassing participants who were demented at the start of the study, those who became demented during follow-up, and participants who remained cognitively unimpaired throughout follow-up. Our cross-sectional findings are consistent with numerous reports that have compared fluency measures at a single testing between participants with AD and unimpaired participants (1-7) and between participants with MCI or preclinical AD and unimpaired participants (2,9-12).

In these cross-sectional analyses, we found that both category fluency and letter fluency differentiated participants with AD from unimpaired participants, with category fluency more impaired than letter fluency in participants with AD at the initial testing. Furthermore, these same patterns are evident in preclinical participants before they develop AD. On their baseline testing, on average 5.4 (range 0.5-9.6) years prior to the conversion to dementia, those who became demented during follow-up were more impaired on category fluency (when measured by naming animals) than participants who remained cognitively intact. However, the two groups did not differ on letter fluency. These findings support the use of category fluency in clinical batteries to detect cognitive impairment that may presage AD.

Few studies have utilized a longitudinal design to examine relative rates of change on different verbal fluency measures. In this current study, we found that, overall, category fluency declined at a faster rate than letter fluency. Although a relatively greater decrement in category compared to letter fluency has been demonstrated in cross-sectional analyses in persons with AD, greater longitudinal declines in category relative to letter fluency have not been previously noted.

The group of participants who subsequently became demented declined on all three fluency measures. This result extends the findings from the Paquid study, where preclinical participants showed greater absolute declines in category fluency from one measurement period to the next compared to non-impaired participants (13).

In the current study, cognitively normal participants also showed faster declines in animal fluency relative to letter fluency over the follow-up period. Declines in category fluency with normal aging have been reported in one other study (16). We extend these findings to show different rates of decline in semantic versus phonemic fluency. These results taken together suggest that greater loss of category compared to letter fluency may be a feature of normal aging that is accelerated with incipient and prevalent AD.

The difference between category fluency and letter fluency performance in AD patients is generally attributed to impairments in semantic memory processes that occur early in the course of AD. Our findings are consistent with the suggestion that the preclinical individuals may already have deterioration in the temporal/parietal area, since animal naming would be associated with the temporal/parietal part of the brain, while FAS would be associated with the frontal lobes (20,21).

We add two further comments about our finding of declines in category fluency in the cognitively normal group, given the relative stability of semantic memory in normal aging (22). First, it is difficult to separate normal aging from disease. Despite remaining unimpaired throughout follow-up, it is possible that this group included some participants whose scores were influenced by preclinical AD changes, given the long subclinical period that characterizes AD, or by impending death (23). Second, verbal fluency tests rely on a combination of cognitive capacities, including semantic memory but also various executive skills with respect to organizing the retrieval process responses (24).

The major strength of this study is the longitudinal testing utilizing standard fluency measures in a well-characterized cohort, who were tested repeatedly over a relatively long period of follow-up. This repeated testing allowed identification of a sub-sample who were cognitively intact at baseline but progressed to dementia. A second strength is the large sub-sample of cognitively intact participants who provided a normative sample of longitudinal change in fluency for comparison to prevalent and preclinical AD samples. Major limitations include the fact that this was a sample of convenience, such that results may not be completely generalizable. Second, although the addition of the preclinical AD sample added novel data in comparison to existing literature in this area, the number of participants in this sample was small. Longer follow-up on this sub-sample of participants who developed AD would have been useful to determine if differences in fluency relative to cognitively normal participants might be apparent at relatively longer periods prior to conversion to dementia. However, although not always statistically significant, the patterns of cross-sectional and longitudinal differences among the fluency measures in this sample of participants who developed AD were consistent with those of the prevalent AD sample.

In summary, our findings support the observation of selective impairment in semantic processes, and suggest that this difference may become evident in normal elderly even before the earliest stages of AD. Our longitudinal data, representing repeated evaluations of letter and category fluency over a group average of 2.3 to 5.9 years, confirm cross-sectional data and show greater longitudinal declines in category compared to letter fluency. Longitudinal declines in fluency also differentiate unimpaired participants from those who will develop AD.

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Figure 1. Comparison of average initial standardized letter and category fluency scores among three groups ($p < 0.0001$ for between-group comparison for all three verbal fluency measures)

Figure 2.

Comparison of annual rate of change for standardized letter and category fluency scores among three groups ($p < 0.0001$ for between-group comparison for all three verbal fluency measures)

Table 1

Sample demographics and baseline fluency measures

	Cognitively normal (n=96)	Preclinical AD (n=21)	Prevalent AD (n=122)	p-value*
Female	61 (63.5%) [†]	14 (66.7%)	67 (54.92%)	0.34
Age at initial test	74.4 (8.5)	80.5 (7.4)	75.5 (7.0)	0.005
Years since AD onset			4.9 (2.8)	
Years of education	14.1 (2.9)	14.1 (2.9)	13.2 (3.3)	0.07
Race				
Caucasian	91 (95%)	21 (100%)	90 (74%)	<0.0001
African-American	2 (2%)	0 (0%)	8 (7%)	
Latino	1 (1%)	0 (0%)	20 (16%)	
Asian/Other	2 (2%)	0 (0%)	4 (3%)	
MMSE	28.9 (1.3)	27.9 (1.8)	18.0 (5.2)	<0.0001
Span of years tested	5.9 (4.3)	4.8 (2.9)	2.3 (1.8)	<0.0001
Number of tests	6.3 (3.9)	5.8 (2.5)	4.5 (3.3)	0.0007
Initial Verbal Fluency: Raw score				
Letter	40.6 (13.2)	37.1 (9.5)	19.8 (12.1)	<0.0001
Pair-wise comparison	0.25 [‡]	<0.0001 [§]	<0.0001 [¶]	
Animal	19.7 (4.8)	15.4 (4.6)	7.9 (4.2)	<0.0001
Pair-wise comparison	0.0001 [‡]	<0.0001 [§]	<0.0001 [¶]	
Supermarket	25.1 (6.4)	20.2 (6.0)	10.1 (5.2)	<0.0001
Pair-wise comparison	0.0043 [‡]	<0.0001 [§]	<0.0001 [¶]	

* P-values from ANOVA for continuous variables and Chi-square test for categorical variables.

[†] Mean (SD) or N(%)

[‡] P-value, Cognitively normal vs. Preclinical AD

[§] P-value, Preclinical AD vs. Prevalent AD

[¶] P-value, Cognitively normal vs. Prevalent AD

Table 2

Group comparisons on average initial performance (cross-sectional, in SD units) and annual rates of change (longitudinal, in SD units/year) from multivariate mixed effect models for standardized letters, animals and supermarket scores*.

Fluency Measure	Group	Mean	SE	P-value for Group Comparison
Letter	Cross-Sectional			<.0001
	Prevalent AD	-1.74	0.12	N, P
	Preclinical AD	-0.32	0.22	
	Cognitively normal	-0.18	0.13	
	Longitudinal			<.0001
	Prevalent AD	-0.24	0.03	N, P
	Preclinical AD	-0.10	0.03	N
	Cognitively normal	-0.01	0.02	
Animals	Cross-Sectional			<.0001
	Prevalent AD	-2.23	0.10	N, P
	Preclinical AD	-0.55	0.19	N
	Cognitively normal	0.05	0.11	
	Longitudinal			<.0001
	Prevalent AD	-0.25	0.03	N, P
	Preclinical AD	-0.15	0.03	N
	Cognitively normal	-0.05	0.02	
Supermarket	Cross-Sectional			<.0001
	Prevalent AD	-2.60	0.12	N, P
	Preclinical AD	-0.64	0.21	
	Cognitively normal	-0.39	0.12	
	Longitudinal			<.0001
	Prevalent AD	-0.29	0.04	N, P
	Preclinical AD	-0.14	0.05	N
	Cognitively normal	-0.02	0.03	

N – indicates significantly different from cognitively normal group

P -- indicates significantly different from preclinical AD group

* Analysis by mixed linear models, with adjustment for age, gender and education (main effects and interactions with follow-up time).

Table 3

Comparisons among fluency measures of initial performance (cross-sectional, in SD units) and annual rates of change (longitudinal, in SD units/year) by study group *

Group	Fluency Measure	Mean	SE	P-value for Comparison among Fluency Measures
Cognitively normal (n=96)				
	Cross-Sectional			0.07
	Supermarket	-0.67	0.16	
	Animal	-0.58	0.15	L
	Letter	-0.72	0.15	
	Longitudinal			0.01
	Supermarket	-0.01	0.03	
	Animal	-0.02	0.03	L
	Letter	0.01	0.03	
Preclinical AD (n=21)				
	Cross-Sectional			0.11
	Supermarket	-0.57	0.18	
	Animal	-0.73	0.16	L
	Letter	-0.44	0.16	
	Longitudinal			0.49
	Supermarket	-0.07	0.03	
	Animal	-0.11	0.02	
	Letter	-0.09	0.02	
Prevalent AD (n=122)				
	Cross-Sectional			<.0001
	Supermarket	-2.55	0.14	L
	Animal	-2.49	0.14	L
	Letter	-1.98	0.14	
	Longitudinal			<.0001
	Supermarket	-0.15	0.05	L
	Animal	-0.14	0.05	L
	Letter	-0.07	0.05	

L – indicates significantly different from Letter fluency.

A – indicates significantly different from Animal fluency.

* Analysis by mixed linear models.